R E M A R K S

Telephone Interview with the Examiner

Claims 13, 15 and 17 were objected to in item No. 7 on page 2 of the June 3, 2008 Office Action (on the Office Action Summary). However, the remainder of the June 3, 2008 Office Action did not include any objection to the claims. The undersigned called Examiner Webb regarding this matter, and Examiner Webb said he did not intend to object to claims 13, 15 and 17.

Claim Amendments

Claims 6 and 12 were amended to recite an "aqueous" ophthalmic solution. This amendment is supported in the specification by the Examples on pages 5 to 7 and 11 to 12. These Examples require the use of water.

Presently Claimed Invention

Applicants' claim 6 relates to an aqueous ophthalmic solution comprising 0.001 to 0.01% (W/V) latanoprost as an active ingredient, wherein the latanoprost is stabilized to be stored at room temperature by adding ε-aminocaproic acid to the solution.

Applicants' claim 12 pertains to an aqueous ophthalmic solution comprising 0.001 to 0.01% (W/V) latanoprost as an active ingredient, wherein the latanoprost is stabilized to be stored at room temperature by adjusting the pH of the solution to 5.0 to 6.25 and adding ε-aminocaproic acid to the solution.

In summary, applicants' present claims are directed to an aqueous ophthalmic solution comprising latanoprost as a active ingredient, wherein the latanoprost is stabilized to be stored at room temperature by (i) adding ε-aminocaproic acid to the solution or (ii) by adjusting the pH of the solution to 5 to 6.25 and adding ε-aminocaproic acid to the solution.

Anticipation Rejection under 35 USC 102

Claims 1 and 5 were rejected under 35 USC 102 as being anticipated by USP 6,011,062 to Schneider et al. for the reasons set forth on page 3 of the June 3, 2008 Office Action.

Claims 1 and 5 were canceled hereinabove. Accordingly, the anticipation rejection is now moot. Withdrawal of the 35 USC 102 rejection is thus respectfully requested.

Obviousness Rejection under 35 USC 103

Claims 6 to 17 were rejected under 35 USC 103 as being unpatentable over USP 6,011,062 to Schneider et al. and further in view of USP 5,556,848 to Kimura et al. for the reasons indicated on pages 4 to 5 of the June 3, 2008 Office Action.

It was admitted in the June 3, 2008 Office Action that Schneider et al. differ from the instant claims insofar as Schneider et al. do not teach adding ε-aminocaproic acid to an ophthalmic solution.

It was further admitted in the June 3, 2008 Office Action that Kimura et al. do not teach the use of latanoprost.

It was asserted in the June 3, 2008 Office Action that Schneider et al. (USP 6,011,062) teach storage-stable prostaglandin compositions and disclose that the use of polyethoxylated castor oils in their compositions enhances the chemical stability of the prostaglandins in their compositions (column 1, lines 52 to 56). It was further asserted in the June 3, 2008 Office Action that it is obvious from Kimura et al. (USP 5,556,848) to use ε-aminocaproic acid instead of using the polyethoxylated caster oils for the purpose of enhancing the chemical stability of latanoprost.

Applicants respectfully disagree with the 35 USC 103 rejection for the following reasons.

Kimura et al. (USP 5,556,848) disclose an ophthalmic suspension comprising difluprednate. Kimura et al. also disclose that a water soluble polymer is added for enhancing dispersion stability in the ophthalmic suspension containing water-insoluble difluprednate (column 2, lines 27 to 37). Kimura et al. disclose that nonionic surfactants, such as polyoxyethylene hydrogenated castor oils can be added in their suspension for enhancing the dispersion stability (column 3, lines 34 to 49). Moreover, Kimura et al. disclose in column 3, lines 19 to 33 that acetates and ε-aminocaproic acid are useful as buffers to suppress formulation of agglomerates, prevent the lowering of pH, and provide a suspension superior in redispersibility and stability.

As discussed above, Kimura et al. teach enhancing the dispersion stability in an ophthalmic suspension containing water-insoluble difluprednate (physical stabilization). In contrast thereto, applicants' present claims 6 to 11 relate to enhancing the chemical stability of latanoprost dissolved in water (chemical stabilization). In other words, since the problem sought to be resolved in Kimura et al. was to stabilize

the dispersion of the suspended ophthalmic solution, whereas that of the presently claimed invention is directed to chemically stabilizing the active ingredient (latanoprost) in a water-soluble ophthalmic solution, Kimura et al. and the presently claimed invention substantially differ from each other in what is stabilized.

Moreover, as discussed hereinabove, Schneider et al. teach storage-stable prostaglandin compositions and disclose that the use of polyethoxylated castor oils in the compositions enhances the chemical stability of the prostaglandins in the compositions (column 1, lines 52 to 56). Further, Figs. 2 and 3 of Schneider et al. show that the addition of polyethoxylated castor oils (Cremophor® EL, Alkamuls® EL-620) increases the chemical stability of prostaglandin (Compound No. 2) as compared with the case where a surfactant (Polysorbate 80) is added.

However, the polyethoxylated castor oil used in Schneider et al. is a polymer classified as a PEG-5 to PEG-200 hydrogenated castor oil, whereas ε-aminocaproic acid used in the presently claimed invention is a low-molecular compound represented by the following formula: $H_2NCH_2CH_2CH_2CH_2COOH$. Polyethoxylated castor oil used in Schneider et al. and ε-aminocaproic acid recited in

applicants' claims completely differ from each other in their chemical structure and their chemical properties.

Further, since the active principle of Kimura et al. is difluprednate, whereas the active ingredient of the presently claimed invention is latanoprost, Kimura et al. and the presently claimed invention completely differ from each other also in the chemical structure and the chemical properties of the respective active ingredient.

Furthermore, although Kimura et al. disclose that ε-aminocaproic acid enhances the dispersion stability of their suspended ophthalmic solution, there is no teaching or suggestion in Kimura et al. of the chemical stability of the active ingredient in a water-soluble ophthalmic solution.

The present specification on pages 12 to 15 describes, in the stability tests of latanoprost, the residual ratio of latanoprost after storage at a temperature range of 50°C to 80°C for the period of 4 to 8 weeks. In the field of ophthalmic solutions, the storage-stability of a drug at room temperature over along period is generally presumed from an accelerated test conducted at a high temperature. Therefore, applicants' present

claims are consistent with the disclosure of the present specification.

In view of the above, it is respectfully submitted that one of ordinary skill in the art would not arrive at the presently claimed invention (i.e., adding ε-aminocaproic acid to enhance the chemical stability of latanoprost) based on the disclosures of Schneider et al. and Kimura et al.

It is therefore respectfully submitted that applicants' claims 6 to 11 patentably distinguish over the references, singly or combined.

Applicants' claims 12 to 17 relate to a further enhancement of the chemical stability of latanoprost by adding ε-aminocaproic acid within a specified pH range of 5.0 to 6.25. As discussed in the preceding paragraph, applicants' claims 6 to 11 are considered to be patentable over the references. Therefore, applicants' claims 12 to 17, characterized by specifying a pH range of 5.0 to 6.25, are also considered to be patentable over the references, singly or combined.

Table 3 on page 16 of the present specification (which is reproduced hereinbelow) shows that after storage at 50°C for 8 weeks, the residual ratio of the latanoprost in an ophthalmic

solution is 93.1% when ε-aminocaproic acid is added to the solution. Moreover, Table 3 shows that after storage at 80°C for 4 weeks, the residual ratio of latanoprost is 51.8% when ε-aminocaproic acid is added, whereas the residual ratio of latanoprost is 6.3 to 28.9% when ε-aminocaproic acid is not added. Thus, applicants' Table 3 clearly shows that the stability of latanoprost in an aqueous ophthalmic solution is significantly improved when ε-aminocaproic acid, out of numerous additives, is added.

Table 3

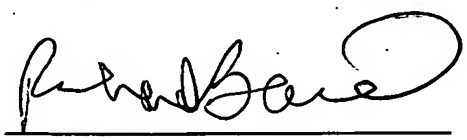
	Additives	Storage at 50 °C for eight weeks	Storage at 80°C for four weeks
Formulation 1	Crystalline sodium dihydrogenphosphate	88.7%	24.0%
Formulation 2	PEG 400	88.8%	25.9%
Formulation 3	Propylene glycol	88.1%	26.1%
Formulation 4	Trehalose	83.7%	26.4%
Formulation 5	Isopropanol	88.9%	28.9%
Formulation 6	α-Cyclodextrin	86.6%	22.1%
Formulation 7	Citric acid	87.1%	6.3%
Formulation 8	ε-Aminocaproic acid	93.1%	51.8%

Withdrawal of the 35 USC 103 rejection is therefore respectfully requested.

Reconsideration is requested. Allowance is solicited.

If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the undersigned at the telephone number given below for prompt action.

Respectfully submitted,



Frishauf, Holtz, Goodman
& Chick, P.C.
220 Fifth Ave., 16th Floor
New York, NY 10001-7708
Tel. No.: (212) 319-4900
Fax No.: (212) 319-5101
E-Mail Address: BARTH@FHGC-LAW.COM
RSB/ddf

Richard S. Barth
REG. NO. 28,180

Enc.: PETITION FOR EXTENSION OF TIME